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Differences in cardiovascular safety with non-steroidal anti-inflammatory drug therapy - a nationwide study in patients with osteoarthritis

Running title: NSAID use and cardiovascular risk in osteoarthritis

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Conflict of interest

The authors declare no conflict of interest.

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ABSTRACT

Osteoarthritis (OA) and the non-steroidal anti-inflammatory drugs (NSAIDs) used to relieve OA-associated pain have been linked independently to increased cardiovascular risk. We examined the risk of cardiovascular events associated with NSAID use in patients with OA. We employed linked nationwide administrative registers to examine NSAID use between 1996 and 2015 by Danish patients with OA aged ≥18 years. Using adjusted Cox proportional hazard analyses, we calculated the risk of the composite outcome of cardiovascular death, non-fatal myocardial infarction and non-fatal ischaemic stroke/TIA, and of each outcome separately, up to 5 years after OA diagnosis. Of 533,502 patients included, 64.3% received NSAIDs and 38,226 (7.2%) experienced a cardiovascular event during follow-up. Compared with non-use, all NSAIDs were associated with increased risk of the composite outcome: hazard ratio (HR) for rofecoxib, 1.90 [95% Confidence Interval, 1.74–2.08]; celecoxib, 1.47 [1.34-1.62]; diclofenac, 1.44 [1.36–1.54]; ibuprofen, 1.20 [1.15–1.25]; naproxen, 1.20 [1.04–1.39]. Similar results were seen for each outcome separately. When celecoxib was used as reference, ibuprofen (HRs 0.81 [CI 0.74-0.90]) and naproxen (HRs 0.81 [0.68-0.97])

exhibited a lower cardiovascular risk, even when low doses were compared. Low-dose naproxen and ibuprofen were associated with the lowest risks of the composite outcome compared to no NSAID use: HRs 1.12 [1.07-1.19] and 1.16 [0.92-1.42], respectively.
In patients with OA, we found significant differences in cardiovascular risk among NSAIDs. Naproxen and ibuprofen appeared to be safer compared to celecoxib, also when we examined equivalent low doses. In terms of cardiovascular safety, naproxen and ibuprofen, at the lowest effective doses, may be the preferred first choices among patients with OA needing pain relief.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used medications [1]. Nevertheless, since the publication of the VIGOR (Vioxx gastrointestinal outcomes research) study in 2000 [2], concerns about the cardiovascular safety of NSAID have led to intense investigations of both selective and non-selective of NSAIDs'. [3-5]
Osteoarthritis (OA) is the most common form of joint disease worldwide, [6] as well as a leading cause of chronic pain, disability and reduced quality of life resulting in a considerable burden to society [7]. Still, NSAIDs are the cornerstone for effective pain management of patients with OA. [8, 9] OA and cardiovascular disease share diverse risk factors, such as ageing, obesity and physical inactivity. [10] Moreover, patients with OA have a high prevalence of cardiovascular risk factors such as hypertension, diabetes and hypercholesterolaemia; [11] hence, they carry an elevated cardiovascular hazard and are potentially more susceptible to cardiovascular adverse effects of NSAIDs than the general population. [12]
NSAIDs provide their analgesic, antipyretic and anti-inflammatory effects through the inhibition of the enzyme cyclooxygenase, which catalyzes the rate-limiting step in the formation of prostanoids, prostaglandins and thromboxane A2. [12] The harmful cardiovascular

effect seems to be shared by all the drugs of this group. [13] Nonetheless, differences in pharmacokinetic and pharmacodynamic characteristics suggest drug-specific cardiovascular profiles. [12]

The FDA (Food and Drug Administration)-mandated PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety Vs Ibuprofen or Naproxen) trial, undertaken while celecoxib remained on the market, aimed to elucidate the comparative cardiovascular safety of celecoxib, ibuprofen and naproxen in patients with arthritis. [14]

The results of PRECISION are challenging to interpret owing to their numerous limitations. [12, 15-17] Conflicting opinions and debate remains about the cardiovascular profile and safety of celecoxib, ibuprofen and naproxen, especially at different dosages, in OA. This prompted us to examine an unselected cohort of patients with OA where we focused on risk of cardiovascular death, acute myocardial infarction (MI) and ischaemic stroke associated with the use of NSAIDs aiming to demonstrate whether differences existed between the individual drugs and their doses.

Materials and Methods

The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies. [18]

Data sources

In Denmark, every resident has a permanent and unique civil registration number that permits linkage between administrative registries. All hospital admissions have been recorded since 1978 in the Danish National Patient Registry with one primary diagnosis and one or more secondary diagnoses, encoded according to the International Classification of Diseases (ICD), until 1994 the ICD-8 and from 1994 the ICD-10. The Danish National Prescription Registry

has since 1995 registered all prescriptions from pharmacies in Denmark and every drug is classified by the Anatomical Therapeutical Chemical (ATC) system. The Central Person Registry comprises information about vital and migration status. The National Causes of Death Register contains the cause of death registered using the ICD-10 classification system.

Study population

This nationwide cohort study includes all adult patients, aged ≥18 years with first contact with the Danish health care system (both hospitalization and ambulatory) for OA between 1 January 1996 and 31 December 2015.

We started follow-up 7 days after the discharge or out-patient contact (index date) until one of the following events (whichever came first): emigration, death, outcome of interest (cardiovascular death, non-fatal ischaemic stroke or MI), 5-year follow-up after index date or end of study period (31 December 2015). Patients were included in the analysis only if they were alive and had not yet experienced the outcomes of interest at the index date.

Non-steroidal Anti-Inflammatory Drug Use

We identified all claimed prescriptions for NSAIDs (ATC M01A, excluding M01AX05 glucosamine) from the Danish National Prescription Registry after the index date. The most commonly used selective cyclooxygenase-(COX) 2 inhibitors, rofecoxib and celecoxib, and the most commonly used non-selective NSAIDs, ibuprofen, diclofenac and naproxen, were analysed separately. All other NSAIDs were analysed in a common group defined as 'other NSAIDs' (Supplementary table 1).

Dose and Duration of Treatment

The national prescription registry does not include information on the prescribed daily dosage of medications. Accordingly, the daily dosage was determined at each new dispensed prescription by calculating average dose from up to three consecutive prescriptions prior to the actual one. For each prescription, the number of tablets dispensed was divided by the estimated daily dosage to calculate the treatment duration. This approach also allowed the dose to increase if subsequent prescriptions were filled before tablets were consumed. If tablets were still available for consumption based on the approximation of exposure at the time of a new prescription for the same NSAID, exposure was defined as an uninterrupted treatment episode. The approximation of drug exposure was based on continuous assessment of new prescriptions during exposure and not on future prescriptions; hence, exposure was not conditioned on future use. If only one prescription was registered for a patient, the daily dosage was estimated as the minimum recommended dosage. Discontinuation of the prescribed NSAID was defined as the point when patients had no more medication available. Patients were allowed to change the NSAID treatment regimen during the study period. Therefore, exposure to NSAIDs was included as a time-dependent variable in the models. The patients were permitted to be in only one drug exposure group at a time but could change groups. If a patient was exposed to more than one NSAID at the same time, we defined a sequence of use (rofecoxib, celecoxib, diclofenac, naproxen, other) to allow all explanatory variables in one model. The baseline NSAID treatment was defined as availability of tablets from seven days after hospital discharge or outpatient contact for OA to six months before. The method we employed has been described in detail in an online document and has been previously applied in other studies from our group. [19-24]

High dose was defined as being above the upper limit of the recommended minimal dose for each drug [25, 26]: ibuprofen >1200 mg; diclofenac >100 mg; naproxen >500 mg; rofecoxib >25 mg; and celecoxib >200 mg.

Comorbidity and concomitant medication

The Ontario acute MI mortality prediction rule modified for the ICD-10 was used to identify comorbidity [27]. Also, we identified discharge diagnoses up to 5 years before the index date. Concomitant use of β-blockers, angiotensin-converting enzyme inhibitors/angiotensin 2 receptor blockers, statins, weak and strong opioids, and anti-diabetic drugs, the latter a proxy for prevalence of diabetes [28], was defined as claimed prescriptions within 180 days before index date.

The exposure status to aspirin was continually updated during the follow-up period. We also identified joint replacement surgery (knee or hip alloplasty) and bone fractures during the follow-up period. In fact, patients with OA have an enhanced risk of undergoing alloplasty and fractures, which lead to augmented pain and so augmented use of painkillers. The codes used to identify comorbidity and medication are listed in Supplementary table 2.

Outcome measures

The primary outcome was a composite of cardiovascular death, non-fatal MI and non-fatal ischaemic stroke/transient ischemic attack. The three endpoints were also analysed separately. The diagnosis of MI in the Danish registries has previously been validated with a positive predictive value of 92 to 100% [29]. Stroke was defined as cerebral infarction, unspecified stroke and transient ischaemic attack: this diagnosis has also been formerly validated with a positive predictive value of 97% [30, 31]. The outcome cardiovascular death was defined as a combination of coronary death or death caused by thromboembolic events

(ischaemic stroke, transient ischaemic attack or arterial embolism) as done previously [32]. Details on ICD codes used to classify the outcomes are listed in the Supplementary material (Supplementary table 2).

Statistical Analysis

We calculated crude incidence rates as number of events per 100 person years for the composite outcome of cardiovascular death, non-fatal MI and non-fatal ischaemic stroke according to NSAID-treatment. We estimated the effects of the different NSAIDs on the outcomes using adjusted Cox regression models in terms of hazard ratios (HRs) and 95% confidence intervals. Exposure to NSAIDs was included as a time-dependent variable in the models, ensuring that patients were only considered at risk when exposed to the respective drug. Each patient could have multiple independent treatment courses with the same drug but also with different drugs. Hence, current NSAID use was specifically compared with non-current NSAID use in our main analyses. Similarly, in additional analyses, we used ibuprofen and celecoxib, overall and at low dose, as reference. Finally, we performed a series of additional subanalyses in which 1) we stratified by the localization of OA (knee, hip or spine), we included only individuals 2) with and without previous cardiovascular disease i.e. patients with and without MI, ischaemic heart disease, stroke or PAD, respectively, 3) new users of NSAIDs (defined as not exposed to NSAIDs during the six months before the index date) and 4) who underwent joint replacement surgery during follow-up.

All models were adjusted for age, sex, concomitant medication and comorbidity as listed in Table 1. Bone fractures and aspirin use were included as a time-dependent variable.

We also determined how the use of these drugs changed during the study period by calculating the number of patients who were in treatment with the various NSAIDs as percentage of the total included population.

Lastly, we performed Schneeweiss analyses [33] to assess how strong an unmeasured confounder, unbalanced distributed between the two compared groups, should be to fully explain the observed findings.

We used Stata statistical package, version 14 (Stata-Corp LP) for the Cox proportional hazards analysis with time-dependent variables and incidence rates. The rest of the statistical analyses and data management were performed using the SAS statistical Software package, version 9.2 (SAS Institute, NC, USA).

Ethics

The Danish Data Protection Agency approved the study (No. 2007–58-015/ GEH-2014-018 I-Suite number: 02736). Cohort studies based on data from administrative registers do not require ethical approval in Denmark.

Results

Characteristics

The study population comprised 533,502 people with a median age of 62.2 years (Standard deviation, SD, 14.3). 343,169 (64.3%) claimed at least one prescription for NSAID during a follow-up of a mean of 3.9 (SD, 1.6) years (2.2 [SD 1.5] in patients who experienced the composite outcome and 4.0 [SD 1.5] in those without). Patients taking non-selective NSAIDs were younger and more often men compared with patients taking the selective COX-2 inhibitors rofecoxib and celecoxib. Patients not taking NSAID had overall more comorbidities compared to those taking them. A detailed description of baseline characteristics of the study cohort is shown in Table 1. During the study period, 38,226 (7.2%) individuals experienced the composite outcome. Among 5266 patients, this occurred during NSAID treatment. The average daily dosage and average duration treatment were 25.4

mg and 31.6 days for rofecoxib, 239.2 mg and 38.9 days for celecoxib, 814.8 mg and 38.8 days for naproxen, 1295.4 mg and 32 days for ibuprofen and 100.3 mg and 37.1 days for diclofenac. We also computed daily dosages for chronic users (>90 days) since the accuracy of our estimates becomes better with continued use: the estimates were similar (Supplementary table 3). Moreover, we calculated the average daily dosage and average treatment duration in patients receiving low and high dosage, respectively: we observed that the doses were comparable - for all the drugs they fell just under the threshold that we chose for definition of the category; notably, naproxen at low dosage was prescribed for a longer period compared to the other NSAIDs (Supplementary table 3).

NSAID use over time

Regarding the use of NSAID during the study period (Fig. 1), ibuprofen has long been the most prescribed NSAID in Denmark with a progressive increase since 2004-2005. The prescription of naproxen in Denmark has remained stable and low during the last 20 years. The overall use of NSAIDs in patients with OA has remained stable at around 30% in recent years.

Main analyses

In the adjusted model, the overall NSAID use was associated with increased hazard ratio (HR) 1.31 (95% confidence interval [CI] 1.27–1.35), compared to no NSAID treatment (Fig. 2). When studied individually, all the examined NSAIDs were associated with elevated risk of the composite outcome compared to no NSAID use. Similar results were seen when fatal and non-fatal ischaemic stroke and MI and cardiovascular death were analysed separately (Fig. 2).

In the dose-related analyses, a dose-dependent increase in risk was seen for the composite outcome with the individual NSAIDs (Fig. 3). Low dose of the non-selective NSAIDs, naproxen and ibuprofen were associated with the lowest risks regarding the composite outcome (HRs 1.12 [1.07-1.19] and 1.16 [0.92, 1.42], respectively), compared to no NSAID treatment (Fig. 3). When MI and stroke were examined separately (Supplementary figure 1A and 1B), we obtained comparable results. Low dosages of naproxen and ibuprofen were not significantly associated with increased risk of cardiovascular death (Supplementary figure 1C) compared to no NSAID treatment.

Additional analyses

Ibuprofen as reference

When compared to ibuprofen (Fig. 4), only naproxen showed a similar cardiovascular risk profile: rofecoxib, celecoxib (not for stroke) and diclofenac were associated with greater cardiovascular risk. When low-dose ibuprofen (≤1200mg) was used as comparator (Supplementary figure 2), rofecoxib, celecoxib and diclofenac had greater HRs for the composite outcome at low and high dosages; conversely, naproxen at any dose seemed to have neutral effects.

Celecoxib as reference

When we performed analyses using celecoxib as reference (Fig. 5), exposure to naproxen and ibuprofen was associated with a significantly lower risk of all cardiovascular outcomes except for stroke. Similarly, we observed increased HRs for the composite outcome for users of low-dose celecoxib (<200 mg) as compared with low-dose ibuprofen and naproxen (Supplementary figure 3).

Subanalyses

Repeating the analyses for the composite outcome stratifying for the localization of OA (knee, hip or spine) did not affect the results (Supplementary figure 4) as well as when we examined separately patients with and without previous cardiovascular disease, respectively (Supplementary figure 5 and 6). We found new users of NSAIDs to be associated with a significantly higher cardiovascular risk of the composite outcome compared to main analysis including both new and prevalent users (Supplementary figure 7). Nevertheless, also among new users, celecoxib had an enhanced cardiovascular hazard compared to ibuprofen and naproxen (Supplementary figure 7B and 7C).

The results of the Schneeweiss analysis indicated that the presence of an unmeasured confounder, or a combination of confounders, unbalanced distributed in the two compared groups by a 17% factor (the overall incidence of obesity in Denmark [34]), had to increase the risk: 1) by a factor of 3.0 to 3.5 in the comparison between NSAID users vs non-NSAID users and 2) by a factor of 2.0 to 2.5 in the comparison between celecoxib users and ibuprofen users to explain the increased risk observed (Supplementary figure 8 and 9).

Patients who underwent join replacement surgery

During the follow-up period, 105,606 patients (19.8%) underwent joint replacement surgery, 80 483 of whom were in the NSAID group. When we evaluated HRs for the composite outcome in the perioperative period, exposure to any NSAIDs was related to an elevated risk in the adjusted models compared with no treatment: HR 1.11 [1.04-1.18]. Examining the different NSAIDs individually, the composite outcome increased significantly by rofecoxib 1.44 [1.13–1.83] and diclofenac 1.20 [1.04–1.38] and non-significantly by celecoxib and naproxen, but not by ibuprofen 1.00 [0.91–1.10] (Supplementary figure 10).

Discussion

In this nationwide study of patients with OA, we found significant differences in the cardiovascular profile of individual NSAIDs. All the currently available widely prescribed NSAIDs (ibuprofen, naproxen, diclofenac and celecoxib) were associated with elevated cardiovascular risk. Low-dose naproxen and ibuprofen seemed to be associated with the lowest cardiovascular risk. Compared with these two non-selective NSAIDs, celecoxib showed increased cardiovascular risk, even at a low dose. Our results differ from those of two recent RCTs, PRECISION and SCOT, which found celecoxib to be non-inferior to ibuprofen or naproxen regarding cardiovascular safety. [14, 35]

Pharmacokinetic and pharmacodynamic characteristics

Despite their shared analgesic and anti-inflammatory effects and common mechanisms of action, NSAIDs differ in pharmacokinetic and pharmacodynamic properties; therefore, small but clinically important differences exist in their cardiovascular profile. [36] Celecoxib is a selective COX-2 inhibitor, with less potency but longer half-life compared to diclofenac. [12] Ibuprofen and naproxen inhibit both COX-isoforms: while ibuprofen has a short half-life (about 2-3 hr) and hence yields only a transient and reversible block of the COX-1-mediated production of thromboxane A2, naproxen has a particularly long half-life which permits a sustained suppression of platelet COX-1 activity potentially mimicking the effects of aspirin if dosed on a sustained basis. [12, 37] However, the potential cardioprotective effect of naproxen is difficult to attain outside of a strictly regulated randomized trial and, moreover, its pharmacokinetics is characterized by strong interindividual heterogeneity.

Results in the context of PRECISION

Several characteristics may explain the divergent results between PRECISION and our study. Firstly, different dosages of the three NSAIDs were compared: in PRECISION, the mean daily dose of celecoxib fell into the low dosage group, while in the medium-high for ibuprofen and naproxen.[14, 25] The imbalance was particularly noticeable in patients with OA, since ibuprofen and naproxen dose could be increased to provide sufficient pain relief, while the daily dosage of celecoxib was capped at 200 mg per day due to regulatory restrictions on a per-country basis. [12, 15] The effects of NSAIDs, both on pain relief and on the cardiovascular system, are closely dose-dependent. [12] In PRECISION, the pain control was worse in the celecoxib-group compared with the other two drugs: higher rates of drug discontinuation due to "insufficient clinical response" and less anti-arthritic efficacy.[14] Accordingly, ibuprofen and naproxen were more frequently associated with renal events and hospitalization for hypertension.[14] Since the thrombogenic effect of NSAIDs is related to the degree of COX-2 inhibition, which increases with dose, it is not surprising that PRECISION found celecoxib non-inferior in terms of adverse cardiovascular events compared to the two non-selective NSAIDs. Analysing equipotent doses, we observed that celecoxib, even at low dosages (≤ 200mg), had significantly increased hazard for the composite outcome compared to low doses of naproxen (≤ 500mg) and ibuprofen (≤ 1200mg). Our calculation of the ingested daily dose relied on an algorithm based on pre-defined typical dosages and prior prescription patterns; and it assumed that all reimbursed NSAIDs were taken regularly and at a fixed mean daily dosage between prescriptions, which does not always happen in reality. We found an average overall daily dosage which fell in the medium dose category for all three drugs. [25] Concurrently, celecoxib and naproxen had an average duration treatment of about 38 days and ibuprofen of 32 days. Also, we observed that the largest part of patients took these medications only for short periods of 1-2 weeks, while the mean duration of

treatment in PRECISION in all arms was around 20 months. Therefore, we believe that our calculations reflect more precisely the clinical practice, where NSAIDs are taken intermittently, for short periods, at low or varying dose, and where switch between the various drugs often occur. [13, 38-40]

Secondly, we studied a Danish cohort of patients with OA, while PRECISION was conducted primarily in the USA (>80% subjects) plus 13 different non-European countries. Thirdly, our composite outcome included non-fatal MI, stroke and cardiovascular death and hence was narrower compared to the Antiplatelet Trialists Collaboration (APTC) outcome. Fourthly, the two studies had deeply different designs and related limitations. In our registries, we do not have information about important clinical features (blood pressure, smoking habits, left ventricular ejection fraction); therefore, the effect of unmeasured confounders cannot be completely ruled out. To account for selection differences among diverse NSAIDs, we performed subanalyses including only patients with previous cardiovascular diseases, which confirmed the main results. Moreover, our Schneeweiss analyses demonstrated that an unmeasured confounder must be particularly strong to fully explain our results and the existence of such a confounder, when possible, is highly unlikely. However, selective COX-2 drugs, because of their relative gastrointestinal safety, in clinical practice tend to be channelled towards patients with diverse comorbidities, [41] as testified by the imbalance in cardiovascular diseases between patients taking COX-2 selective drugs and non-selective NSAIDs at baseline. Therefore, despite the robustness of our results, the adjustments for comorbidities and the several subanalyses, selection bias and residual confounding may have influenced our findings.

The average relative risk of cardiovascular complications associated with NSAIDs is in the order of 1.0-2.0. Particularly, a large meta-analysis and a systematic review of observational studies found an increased risk of major vascular events for celecoxib at any dose of 1.36

(95% CI 1.00-1.84) and at low dose (≤200 mg/d) of 1.16 (95% CI 1.09-1.47) compared to non-NSAID use, respectively.[26, 42] Therefore, although PRECISION included 24,000 arthritis patients, it could not be powered enough to detect slight disparities in the cardiovascular profile of the three examined NSAIDs. [15, 16] Furthermore, despite the analysis by aspirin status showed no difference in PRECISION, [43] the authors did not update the use of this medication during the study course, only available as a baseline characteristic. The use of aspirin may have changed considerably during the study period because of its long duration (10 years). Notably ibuprofen and naproxen, but not celecoxib, can undermine the cardioprotective effects of aspirin. Moreover, patients most dependent on the platelet-inactivating effect of aspirin, i.e. those with a recent cardiovascular event (<3 months) were excluded. Conversely, we updated continually our analyses according to exposure to aspirin: this could have contributed to the different results. Finally, distinct inclusion criteria may have played an important role on the outcomes and on the findings: for example, patients with severe heart failure or patients taking warfarin were excluded from PRECISION. [44] Similarly, patients in PRECISION had a mean duration since first diagnosis of OA of about 10 years, while we enrolled individuals with first contact with the Danish health care system for OA. [44]

Other studies comparing NSAIDs in patients with OA

Another recent clinical trial, Standard care vs. Celecoxib Outcome Trial (SCOT), conducted in Europe, [35] compared celecoxib with non-selective NSAIDs and did not find differences in cardiovascular risk between the two groups. However, in this study, all the non-selective NSAIDs were grouped together, including diclofenac, which is characterized by a degree of COX-2 selectivity and a cardiovascular-hazard comparable with COX-2 inhibitors [45] and hence may have diluted the result toward non-inferiority of celecoxib. Notably, in our

analyses, diclofenac exhibited a magnitude of risk in accordance with previous studies [5, 46] and a cardiovascular risk profile similar to celecoxib. Moreover, patients taking celecoxib had a higher drop-out rate than those in the non-selective NSAID group, often for a lack of efficacy in pain management. [17] Finally, the on-treatment analysis failed to prove non-inferiority of celecoxib. [12]

The results of our study are strengthened by their concordance with the mechanism by which NSAIDs are supposed to confer cardiovascular hazard [12, 47, 48] and with the conclusions of previous large meta-analyses. [26, 46]

Limitations

With the observational nature of our study, any conclusion must be drawn with caution. The initial symptoms of ischaemic heart disease could be interpreted as musculoskeletal disorder and thereafter progress to myocardial infarction. Although NSAIDs are not recommended for the treatment of coronary heart disease, we cannot completely exclude the possibility that this will happen. Consequently, it is possible that our results overestimate the NSAID-associated risk. However, the association of NSAIDs with cardiovascular hazard is widely reported [2, 26, 46, 49]. We studied an OA cohort, which minimized the risk of confounding-by-indication. Moreover, at baseline, the subjects not taking NSAIDs had an overall higher cardiovascular risk (older age and more comorbidities). It is therefore unlikely that confounding-by-indication alone would drive our results.

In Denmark, from October 2001, ibuprofen, as the only NSAIDs, was available as over-the-counter medicine, but at low dosage (200mg) and small amounts (maximum 100 tablets). However, in the light of the reimbursement obtainable with a prescription, patients requiring higher doses or long-term treatment, such as patients with OA, would have a financial

incentive to obtain prescriptions from their physician. Moreover, restricting the analyses to 1996-2000 did not alter the association between NSAIDs and cardiovascular risk.

Conclusions

This nationwide study of an OA cohort suggests that the use of individual NSAIDs was associated with different levels of cardiovascular risk. As NSAIDs are often used in OA, these differences could have considerable impact on OA patients' disease burden. NSAIDs with stronger COX-1 selective profiles, such as naproxen and ibuprofen, at the lowest effective doses, may be preferred for cardiovascular safety.

References

1. McGettigan P and Henry D. Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle-, and high-income countries. *PLoS Med*. 2013;10:e1001388.
2. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ and Group VS. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med*. 2000;343:1520-8, 2 p following 1528.
3. Farkouh ME, Kirshner H, Harrington RA, Ruland S, Verheugt FW, Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehrsam E, Gitton X, Krammer G, Mellein B, Gimona A, Matchaba P, Hawkey CJ, Chesebro JH and Group TS. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *Lancet*. 2004;364:675-84.
4. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M and Adenoma Prevention with Celecoxib Study I. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med*. 2005;352:1071-80.
5. Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, Reicin AS, Bombardier C, Weinblatt ME, van der Heijde D, Erdmann E, Laine L and Committee MS. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet*. 2006;368:1771-81.
6. Litwic A, Edwards MH, Dennison EM and Cooper C. Epidemiology and burden of osteoarthritis. *Br Med Bull*. 2013;105:185-99.
7. Gupta S, Hawker GA, Laporte A, Croxford R and Coyte PC. The economic burden of disabling hip and knee osteoarthritis (OA) from the perspective of individuals living with this condition. *Rheumatology (Oxford)*. 2005;44:1531-7.
8. Adams SS, McCullough KF and Nicholson JS. The pharmacological properties of ibuprofen, an anti-inflammatory, analgesic and antipyretic agent. *Arch Int Pharmacodyn Ther*. 1969;178:115-29.

9. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, Hawker GA, Henrotin Y, Hunter DJ, Kawaguchi H, Kwoh K, Lohmander S, Rannou F, Roos EM and Underwood M. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage*. 2014;22:363-88.
10. Wang H, Bai J, He B, Hu X and Liu D. Osteoarthritis and the risk of cardiovascular disease: a meta-analysis of observational studies. *Sci Rep*. 2016;6:39672.
11. Puenpatom RA and Victor TW. Increased prevalence of metabolic syndrome in individuals with osteoarthritis: an analysis of NHANES III data. *Postgrad Med*. 2009;121:9-20.
12. Grosser T, Ricciotti E and FitzGerald GA. The Cardiovascular Pharmacology of Nonsteroidal Anti-Inflammatory Drugs. *Trends Pharmacol Sci*. 2017.
13. Bally M, Dendukuri N, Rich B, Nadeau L, Helin-Salmivaara A, Garbe E and Brophy JM. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. *BMJ*. 2017;357:j1909.
14. Nissen SE, Yeomans ND, Solomon DH, Luscher TF, Libby P, Husni ME, Graham DY, Borer JS, Wisniewski LM, Wolski KE, Wang Q, Menon V, Ruschitzka F, Gaffney M, Beckerman B, Berger MF, Bao W, Lincoff AM and Investigators PT. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. *N Engl J Med*. 2016;375:2519-29.
15. FitzGerald GA. Imprecision: Limitations to Interpretation of a Large Randomized Clinical Trial. *Circulation*. 2017;135:113-115.
16. Patrono C and Baigent C. Coxibs, Traditional NSAIDs, and Cardiovascular Safety Post-PRECISION: What We Thought We Knew Then and What We Think We Know Now. *Clin Pharmacol Ther*. 2017;102:238-245.
17. Antman EM. Evaluating the Cardiovascular Safety of Nonsteroidal Anti-Inflammatory Drugs. *Circulation*. 2017;135:2062-2072.
18. Tveden-Nyborg P, Bergmann TK and Lykkesfeldt J. Basic & Clinical Pharmacology & Toxicology Policy for Experimental and Clinical studies. *Basic Clin Pharmacol Toxicol*. 2018;123:233-235.
19. Rytgaard H.C. GTA. https://github.com/tagteam/heaven/blob/master/worg/medicin-macro.pdf

From %x_recepter to Rcpp: a mathematical formulation of the algorithm, a new R-user interface and an e-cient implementation. 2017.
20. Fosbol EL, Gislason GH, Jacobsen S, Abildstrom SZ, Hansen ML, Schramm TK, Folke F, Sorensen R, Rasmussen JN, Kober L, Madsen M and Torp-Pedersen C. The pattern of use of non-steroidal anti-inflammatory drugs (NSAIDs) from 1997 to 2005: a nationwide study on 4.6 million people. *Pharmacoepidemiol Drug Saf*. 2008;17:822-33.
21. Lamberts M, Lip GY, Hansen ML, Lindhardsen J, Olesen JB, Raunso J, Olsen AM, Andersen PK, Gerds TA, Fosbol EL, Torp-Pedersen C and Gislason GH. Relation of nonsteroidal anti-inflammatory drugs to serious bleeding and thromboembolism risk in patients with atrial fibrillation receiving antithrombotic therapy: a nationwide cohort study. *Ann Intern Med*. 2014;161:690-8.
22. Olsen AM, Fosbol EL, Lindhardsen J, Andersson C, Folke F, Nielsen MB, Kober L, Hansen PR, Torp-Pedersen C and Gislason GH. Cause-specific cardiovascular risk associated with nonsteroidal anti-inflammatory drugs among myocardial infarction patients--a nationwide study. *PLoS One*. 2013;8:e54309.
23. Gislason GH, Rasmussen JN, Abildstrom SZ, Gadsboll N, Buch P, Friberg J, Rasmussen S, Kober L, Stender S, Madsen M and Torp-Pedersen C. Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. *Eur Heart J*. 2006;27:1153-8.
24. Olesen JB, Hansen PR, Abildstrom SZ, Andersson C, Weeke P, Schmiegelow M, Erdal J, Torp-Pedersen C and Gislason GH. Valproate attenuates the risk of myocardial infarction in patients with epilepsy: a nationwide cohort study. *Pharmacoepidemiol Drug Saf*. 2011;20:146-53.

25. Chou R, McDonagh MS, Nakamoto E and Griffin J. *Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review* Rockville (MD); 2011.
26. McGettigan P and Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med*. 2011;8:e1001098.
27. Tu JV, Austin PC, Walld R, Roos L, Agras J and McDonald KM. Development and validation of the Ontario acute myocardial infarction mortality prediction rules. *J Am Coll Cardiol*. 2001;37:992-7.
28. Schramm TK, Gislason GH, Kober L, Rasmussen S, Rasmussen JN, Abildstrom SZ, Hansen ML, Folke F, Buch P, Madsen M, Vaag A and Torp-Pedersen C. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. *Circulation*. 2008;117:1945-54.
29. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L and Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-90.
30. Krarup LH, Boysen G, Janjua H, Prescott E and Truelsen T. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology*. 2007;28:150-4.
31. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH and Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2011;342:d124.
32. Lamberts M, Lip GY, Ruwald MH, Hansen ML, Ozcan C, Kristensen SL, Kober L, Torp-Pedersen C and Gislason GH. Antithrombotic treatment in patients with heart failure and associated atrial fibrillation and vascular disease: a nationwide cohort study. *J Am Coll Cardiol*. 2014;63:2689-98.
33. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf*. 2006;15:291-303.
34. Sunhedsstyrelsen - www.sst.dk. 2018:Forekomst af overvægt.
35. MacDonald TM, Hawkey CJ, Ford I, McMurray JJ, Scheiman JM, Hallas J, Findlay E, Grobbee DE, Hobbs FD, Ralston SH, Reid DM, Walters MR, Webster J, Ruschitzka F, Ritchie LD, Perez-Gutthann S, Connolly E, Greenlaw N, Wilson A, Wei L and Mackenzie IS. Randomized trial of switching from prescribed non-selective non-steroidal anti-inflammatory drugs to prescribed celecoxib: the Standard care vs. Celecoxib Outcome Trial (SCOT). *Eur Heart J*. 2016.
36. Grosser T, Fries S and FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. *J Clin Invest*. 2006;116:4-15.
37. Capone ML, Tacconelli S, Sciulli MG, Grana M, Ricciotti E, Minuz P, Di Gregorio P, Merciaro G, Patrono C and Patrignani P. Clinical pharmacology of platelet, monocyte, and vascular cyclooxygenase inhibition by naproxen and low-dose aspirin in healthy subjects. *Circulation*. 2004;109:1468-71.
38. Gore M, Sadosky A, Leslie D, Tai KS and Seleznick M. Patterns of therapy switching, augmentation, and discontinuation after initiation of treatment with select medications in patients with osteoarthritis. *Clin Ther*. 2011;33:1914-31.
39. Sift R, van Staa TP, Abenhaim L and Ebner D. A study of the longitudinal utilization and switching-patterns of non-steroidal anti-inflammatory drugs using a pharmacy based approach. *Pharmacoepidemiol Drug Saf*. 1997;6:263-8.
40. Langman M, Kahler KH, Kong SX, Zhang Q, Finch E, Bentkover JD and Stewart EJ. Drug switching patterns among patients taking non-steroidal anti-inflammatory drugs: a retrospective cohort study of a general practitioners database in the United Kingdom. *Pharmacoepidemiol Drug Saf*. 2001;10:517-24.

41. MacDonald TM, Morant SV, Goldstein JL, Burke TA and Pettitt D. Channelling bias and the incidence of gastrointestinal haemorrhage in users of meloxicam, coxibs, and older, non-specific non-steroidal anti-inflammatory drugs. *Gut*. 2003;52:1265-70.
42. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR and Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ*. 2006;332:1302-8.
43. Reed GW, Abdallah MS, Shao M, Wolski K, Wisniewski L, Yeomans N, Luscher TF, Borer JS, Graham DY, Husni ME, Solomon DH, Libby P, Menon V, Lincoff AM and Nissen SE. Effect of Aspirin Coadministration on the Safety of Celecoxib, Naproxen, or Ibuprofen. *J Am Coll Cardiol*. 2018;71:1741-1751.
44. Becker MC, Wang TH, Wisniewski L, Wolski K, Libby P, Luscher TF, Borer JS, Mascette AM, Husni ME, Solomon DH, Graham DY, Yeomans ND, Krum H, Ruschitzka F, Lincoff AM, Nissen SE and Investigators P. Rationale, design, and governance of Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION), a cardiovascular end point trial of nonsteroidal antiinflammatory agents in patients with arthritis. *Am Heart J*. 2009;157:606-12.
45. Capone ML, Tacconelli S, Di Francesco L, Sacchetti A, Sciulli MG and Patrignani P. Pharmacodynamic of cyclooxygenase inhibitors in humans. *Prostaglandins Other Lipid Mediat*. 2007;82:85-94.
46. Coxib, traditional NTC, Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, Bombardier C, Cannon C, Farkouh ME, FitzGerald GA, Goss P, Halls H, Hawk E, Hawkey C, Hennekens C, Hochberg M, Holland LE, Kearney PM, Laine L, Lanas A, Lance P, Laupacis A, Oates J, Patrono C, Schnitzer TJ, Solomon S, Tugwell P, Wilson K, Wittes J and Baigent C. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet*. 2013;382:769-79.
47. Schmidt M, Lamberts M, Olsen AM, Fosboll E, Niessner A, Tamargo J, Rosano G, Agewall S, Kaski JC, Kjeldsen K, Lewis BS and Torp-Pedersen C. Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology. *Eur Heart J Cardiovasc Pharmacother*. 2016;2:108-18.
48. Varga Z, Sabzwari SRA and Vargova V. Cardiovascular Risk of Nonsteroidal Anti-Inflammatory Drugs: An Under-Recognized Public Health Issue. *Cureus*. 2017;9:e1144.
49. Solomon SD, Wittes J, Finn PV, Fowler R, Viner J, Bertagnolli MM, Arber N, Levin B, Meinert CL, Martin B, Pater JL, Goss PE, Lance P, Obara S, Chew EY, Kim J, Arndt G, Hawk E and Cross Trial Safety Assessment G. Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials: the cross trial safety analysis. *Circulation*. 2008;117:2104-13.

Figure legends

Title: Percentage use of different NSAID among patients with OA (1996-2015)

Figure 1: temporal trend of the use of various NSAIDs among patients with OA during the study period (1996-2015). NSAID, Non-Steroidal Anti-Inflammatory Drugs; OA, osteoarthritis

Title: Risk of all outcomes with usage of specific NSAIDs compared with no NSAID treatment

Figure 2: crude incidence rate and unadjusted and adjusted Cox proportional-hazard ratio of composite outcome, fatal and non-fatal stroke, fatal and non-fatal myocardial infarction and cardiovascular death associated with use of NSAIDs in patients with osteoarthritis. Reference group: no treatment with NSAIDs. NSAID, Non-Steroidal Anti-Inflammatory Drugs. *per 100-person years

Title: Risk of composite outcomes with usage of different NSAID doses compared with no NSAID treatment

Figure 3: crude incidence rate and unadjusted and adjusted Cox proportional-hazard ratio of composite outcome associated with use of NSAIDs in patients with osteoarthritis in accordance with dose of the drugs. Reference group: no treatment with NSAIDs. NSAID, Non-Steroidal Anti-Inflammatory Drugs. *per 100 person years

Title: Risk of all outcomes with usage of specific NSAIDs compared with ibuprofen

Figure 4: crude incidence rate and unadjusted and adjusted Cox proportional-hazard ratio of composite outcome, fatal and non-fatal stroke, fatal and non-fatal myocardial infarction and cardiovascular death associated with use of NSAIDs in patients with osteoarthritis. Reference group: patients taking ibuprofen. NSAID, Non-Steroidal Anti-Inflammatory Drugs. *per 100 person years

Title: Risk of all outcomes with usage of specific NSAIDs compared with celecoxib

Figure 5: crude incidence rate and unadjusted and adjusted Cox proportional-hazard ratio of composite outcome, fatal and non-fatal stroke, fatal and non-fatal myocardial infarction and

cardiovascular death associated with use of NSAIDs in patients with osteoarthritis. Reference group: patients taking celecoxib. NSAID, Non-Steroidal Anti-Inflammatory Drugs. *per 100 person years

Table 1. Baseline Characteristics of the Total Study Population and Individual Treatment Group

Characteristic	Total Population (%)	No NSAID (%)	Overall NSAID (%)	Rofecoxib	Celecoxib	Diclofenac	Ibuprofen	Naproxen	Other NSAIDs
Total patients	533 502 (100)	190 333 (35.7)	343 169 (64.3)	23 011 (4.3)	24 459 (4.6)	90 918 (17.0)	239 901 (45.0)	21 606 (4.0)	80 189 (15.0)
Mean age (SD), y	62.2 (14.3)	63.6 (14.9)	61.4 (13.8)	66.5 (13.2)	65.9 (13.0)	60.3 (13.7)	60.2 (13.8)	60.1 (14.2)	63.1 (13.5)
Women	301 795 (56.6)	104 961 (55.2)	196 834 (57.4)	15 985 (69.5)	16 486 (67.4)	52 079 (57.3)	134 682 (56.1)	12 334 (57.1)	50 148 (62.5)
Men	231 707 (43.4)	85 372 (44.8)	146 335 (42.6)	7026 (30.5)	7973 (32.6)	38 839 (42.7)	105 219 (43.9)	9272 (42.9)	30 050 (37.5)
Comorbidity									
Previous MI	9116 (1.7)	4154 (2.2)	4962 (1.5)	476 (2.1)	452 (1.9)	1301 (1.4)	3147 (1.3)	325 (1.5)	1244 (1.6)
IHD*	37 163 (7.0)	15 877 (8.3)	21 286 (6.2)	1839 (8.0)	1934 (7.9)	5509 (6.1)	13 808 (5.8)	1369 (6.3)	5382 (6.7)
Previous stroke	16 293 (3.1)	7682 (4.0)	8611 (2.5)	790 (3.4)	768 (3.1)	2080 (2.3)	5421 (2.3)	475 (2.2)	2121 (2.6)
PAD	11 439 (2.2)	5168 (2.7)	6271 (1.8)	555 (2.4)	587 (2.4)	1543 (1.7)	4038 (1.7)	396 (1.8)	1550 (1.9)
HF	14 225 (2.7)	7188 (3.8)	7037 (2.1)	787 (3.4)	761 (3.1)	1655 (1.8)	4277 (1.8)	399 (1.9)	1809 (2.3)
AF	20 535 (3.9)	10 885 (5.7)	9650 (2.8)	787 (3.4)	870 (3.6)	2269 (2.5)	6086 (2.5)	583 (2.7)	2199 (2.7)
Diabetes	33 635 (6.3)	13 006 (6.8)	20 629 (6.0)	1029 (4.5)	1204 (4.9)	5132 (5.6)	14 759 (6.2)	1403 (6.5)	4701 (5.9)
Dyslipidemia	82 593 (15.5)	33 894 (17.8)	48 699 (14.2)	1123 (4.9)	1875 (7.7)	10 702 (11.8)	36 694 (15.3)	3118 (14.4)	9710 (12.1)
Hypertension	61 774 (11.6)	21 771 (11.4)	40 003 (11.7)	3672 (16.0)	3701 (15.1)	10 558 (11.6)	26 192 (10.9)	2505 (11.6)	10 480 (13.1)
COPD	17 781 (3.3)	7426 (3.9)	10 355 (3.0)	872 (3.8)	916 (3.8)	2589 (2.9)	6865 (2.9)	628 (2.9)	2568 (3.2)
Malignancy	28 777 (5.4)	12 071 (6.3)	16 706 (4.9)	1303 (5.7)	1372 (5.6)	4178 (4.6)	11 222 (4.7)	955 (4.4)	3777 (4.7)
GI-bleeding	12 705 (2.4)	6011 (3.2)	6694 (2.0)	630 (2.7)	650 (2.7)	1630 (1.8)	4266 (1.8)	408 (1.9)	1623 (2.0)
CKD	7268 (1.4)	3926 (2.1)	3342 (1.0)	204 (0.9)	215 (0.9)	844 (0.9)	2250 (0.9)	221 (1.0)	720 (0.9)
Osteoporose	24 161 (4.5)	10 936 (5.8)	13 225 (3.9)	1004 (4.4)	1177 (4.8)	2749 (3.0)	9053 (3.8)	765 (3.5)	2976 (3.7)
Rheumatologic	18 093	6139	11 954	1333	1386	2882 (3.2)	7192 (3.0)	761 (3.5)	3669

disease	(3.4)	(3.2)	(3.5)	(5.8)	(5.7)				(4.6)
Concomitant medical treatment									
β - blockers	65 641 (12.3)	27 080 (14.2)	38 561 (11.2)	2548 (11.1)	2982 (12.2)	9674 (10.6)	25 900 (10.8)	2462 (11.4)	9376 (11.7)
ACE inhibitors	66 437 (12.5)	25 793 (13.6)	40 644 (11.8)	2025 (8.8)	2429 (9.9)	9450 (10.4)	29 053 (12.1)	2615 (12.1)	8917 (11.1)
ARB	48 718 (9.1)	18 889 (9.9)	29 829 (8.7)	1234 (5.4)	1758 (7.2)	7073 (7.8)	21 521 (9.0)	1780 (8.2)	6694 (8.4)
Weak opioids	128 642 (24.1)	41 829 (22.0)	86 813 (25.3)	7231 (31.4)	7921 (32.4)	23 446 (25.8)	58 996 (24.6)	5454 (25.2)	22 264 (27.8)
Strong opioids	50 869 (9.5)	18 053 (9.5)	32 816 (9.6)	1930 (8.4)	2470 (10.1)	7781 (8.6)	23 094 (9.6)	2165 (10.0)	7557 (9.4)
NSAIDs**	284 337 (53.3)	58 042 (30.5)	226 295 (65.9)	15 966 (69.4)	17 564 (71.8)	63 198 (69.5)	157 064 (65.5)	15 076 (69.8)	58 618 (73.1)
ASA * **	131 186 (24.6)	46 904 (24.6)	84 282 (24.6)	7482 (32.5)	7869 (32.2)	22 650 (24.9)	55 103 (23.0)	5582 (25.8)	22 322 (27.8)
Joint replacement surgery ** **	105 606 (19.8)	25 123 (13.2)	80 483 (23.5)	7232 (31.4)	8217 (33.6)	22 881 (25.2)	53 292 (22.2)	5045 (23.4)	23 638 (29.5)
Bone fractures ** **	55 952 (10.5)	16 644 (8.7)	39 308 (11.5)	3781 (16.4)	3800 (15.5)	11 036 (12.1)	26 949 (11.2)	2414 (11.2)	10 412 (13.0)
Type of OA									
OA of knee	243 848 (45.7)	77 492 (40.7)	166 356 (48.5)	12 350 (53.7)	12 586 (51.5)	45 056 (49.6)	116 843 (48.7)	10 924 (50.6)	42 100 (52.5)
OA of hip	160 369 (30.1)	54 330 (28.5)	106 039 (30.9)	9308 (40.5)	10 349 (42.3)	28 838 (31.7)	68 549 (28.6)	6346 (29.4)	27 834 (34.7)
OA of spine	84 104 (15.8)	27 825 (14.6)	56 279 (16.4)	4498 (19.5)	4377 (17.9)	16 089 (17.7)	39 558 (16.5)	3564 (16.5)	13 552 (16.9)

Abbreviations: MI, myocardial infarction; IHD, ischemic heart disease; PAD, peripheral artery disease; HF, heart failure; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; GI-bleeding, gastrointestinal bleeding; CKD, Chronic kidney disease; ASA, acetylsalicylic acid; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin-2

receptor blockers; NSAID, Nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; operations performed during follow-up period

* previous MI not included

** baseline NSAID treatment was defined as availability of tablets within six months before the inclusion

*** including patients who redeemed prescriptions for aspirin during follow-up

**** during follow-up period

Figure 1

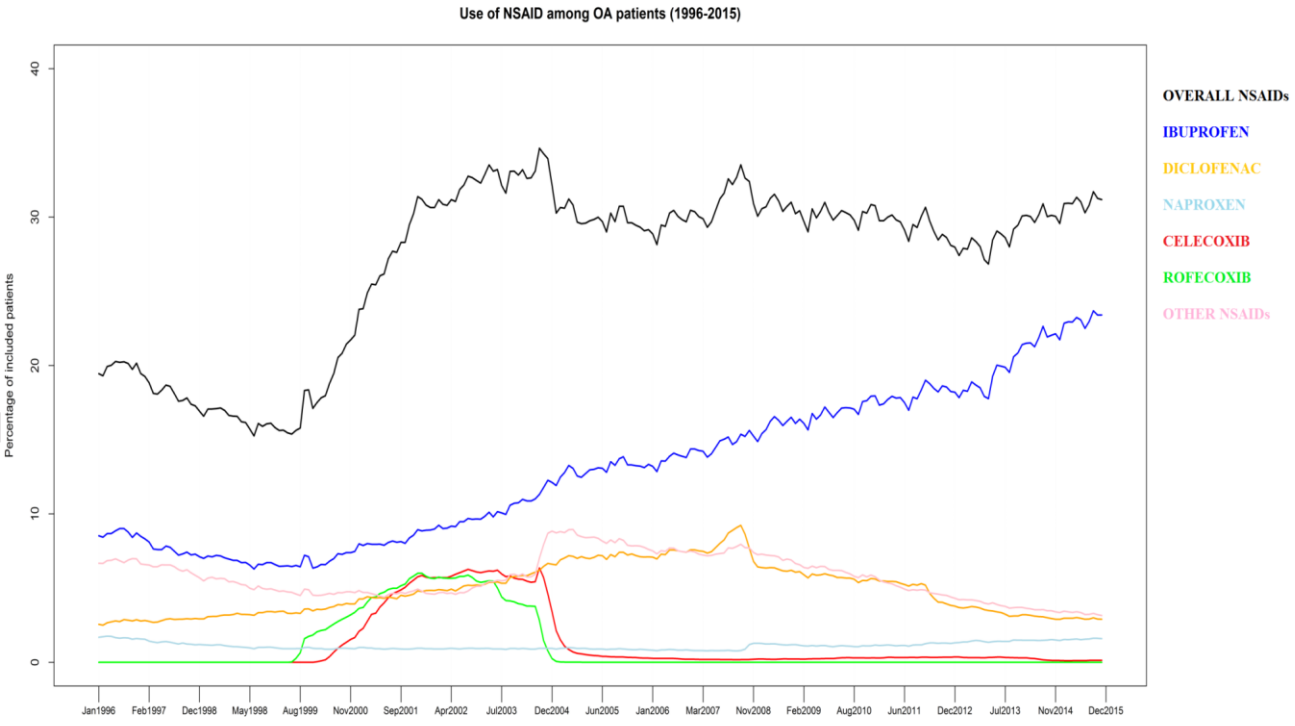

Figure 2

Groups	Events	Person Years	Incidence rate*	Unadjusted HR [95% CI]	Adjusted HR [95% CI]	p-value
Composite outcome						
No NSAID	32960	19000	1.78	Ref.	Ref.	Ref.
Any NSAID	5266	2300	2.29	1.26 [1.23-1.30]	1.31 [1.27-1.35]	<0.001
Rofecoxib	473	97.3	4.86	2.70 [2.46-2.95]	1.90 [1.74-2.08]	<0.001
Celecoxib	444	119	3.73	2.06 [1.88-2.27]	1.47 [1.34-1.62]	<0.001
Diclofenac	1008	439	2.3	1.27 [1.19-1.35]	1.44 [1.36-1.54]	<0.001
Ibuprofen	2074	1100	1.89	1.04 [0.99-1.09]	1.20 [1.15-1.25]	<0.001
Naproxen	181	89.1	2.03	1.12 [0.97-1.30]	1.20 [1.04-1.39]	0.015
Other	1086	459.4	2.37	1.31 [1.23-1.39]	1.22 [1.15-1.31]	<0.001
Fatal and non fatal stroke						
No NSAID	18055	19000	0.97	Ref.	Ref.	Ref.
Any NSAID	2834	2300	1.22	1.25 [1.20-1.30]	1.28 [1.23-1.33]	<0.001
Rofecoxib	264	98.6	2.68	2.74 [2.43-3.10]	1.89 [1.67-2.14]	<0.001
Celecoxib	213	120.3	1.77	1.81 [1.58-2.07]	1.26 [1.10-1.45]	0.001
Diclofenac	528	441.9	1.19	1.22 [1.12-1.33]	1.38 [1.26-1.50]	<0.001
Ibuprofen	1139	1100	1.03	1.05 [0.99-1.11]	1.21 [1.14-1.28]	<0.001
Naproxen	98	89.7	1.09	1.11 [0.91-1.36]	1.18 [1.04-1.44]	0.018
Other	592	462.4	1.28	1.31 [1.21-1.43]	1.20 [1.11-1.30]	<0.001
Fatal and non fatal myocardial infarction						
No NSAID	15504	19000	0.82	Ref.	Ref.	Ref.
Any NSAID	2476	2300	1.06	1.27 [1.22-1.33]	1.34 [1.28-1.40]	<0.001
Rofecoxib	205	99.8	2.05	2.47 [2.15-2.83]	1.80 [1.57-2.06]	<0.001
Celecoxib	211	121.5	1.74	2.08 [1.81-2.38]	1.52 [1.33-1.74]	<0.001
Diclofenac	496	444.2	1.12	1.34 [1.22-1.46]	1.54 [1.41-1.68]	<0.001
Ibuprofen	969	1100	0.87	1.04 [0.98-1.11]	1.21 [1.14-1.29]	<0.001
Naproxen	82	90.2	0.91	1.09 [0.88-1.35]	1.22 [1.08-1.46]	0.020
Other	513	465.6	1.1	1.32 [1.21-1.45]	1.26 [1.16-1.38]	<0.001
Cardiovascular death						
No NSAID	13317	19000	0.7	Ref.	Ref.	Ref.
Any NSAID	1854	2300	0.79	1.12 [1.07-1.17]	1.23 [1.18-1.30]	<0.001
Rofecoxib	200	101.2	1.98	2.79 [2.43-3.21]	1.77 [1.54-2.04]	<0.001
Celecoxib	210	122.7	1.71	2.41 [2.10-2.76]	1.50 [1.31-1.72]	<0.001
Diclofenac	326	447	0.73	1.03 [0.93-1.15]	1.36 [1.22-1.52]	<0.001
Ibuprofen	642	1100	0.58	0.85 [0.75-0.88]	1.06 [0.97-1.14]	0.186
Naproxen	66	90.7	0.73	1.03 [0.81-1.32]	1.23 [0.96-1.56]	0.110
Other	440	468.2	0.88	1.24 [1.13-1.37]	1.17 [1.06-1.29]	0.001

*** per 1000 person years**

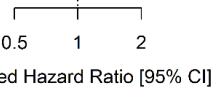

Figure 3

Groups	Events	Person Years	Incidence rate*	Unadjusted HR [95% CI]	Adjusted HR [95% CI]	p-value
Composite outcome						
No NSAID	32960	19000	1.78	Ref.	Ref.	Ref.
Rofecoxib						
≤25mg	421	88.8	4.74	2.63 [2.39-2.90]	1.87 [1.70-2.06]	<0.001
>25mg	52	8.53	6.1	3.37 [2.57-4.42]	2.17 [1.65-2.85]	<0.001
Celecoxib						
≤200mg	294	88.5	3.32	1.83 [1.63-2.06]	1.32 [1.18-1.48]	<0.001
>200mg	150	30.5	4.92	2.73 [2.33-3.21]	1.90 [1.62-2.23]	<0.001
Diclofenac						
≤100mg	778	355.4	2.19	1.21 [1.13-1.30]	1.37 [1.27-1.47]	<0.001
>100mg	230	83.6	2.75	1.52 [1.33-1.73]	1.78 [1.57-2.03]	<0.001
Ibuprofen						
≤1200mg	1478	869.5	1.7	0.94 [0.89-0.99]	1.12 [1.07-1.19]	<0.001
>1200mg	596	227	2.63	1.44 [1.33-1.56]	1.43 [1.32-1.56]	<0.001
Naproxen						
≤500mg	83	38	2.18	1.21 [0.98-1.51]	1.16 [0.92-1.42]	0.204
>500mg	98	51.1	1.92	1.05 [0.86-1.29]	1.23 [1.01-1.48]	0.035
Other						
Low dose	759	342	2.22	1.23 [1.15-1.33]	1.15 [1.07-1.23]	<0.001
High dose	327	117.4	2.79	1.54 [1.38-1.71]	1.45 [1.30-1.62]	<0.001

*** per 1000 person years**

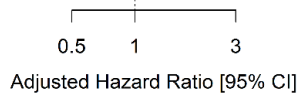

Figure 4

Groups	Events	Person Years	Incidence rate*	Unadjusted HR [95% CI]	Adjusted HR [95% CI]	p-value
Composite outcome						
Ibuprofen	2071	1100	1.89	Ref.	Ref.	Ref.
No NSAID	32960	19000	1.78	0.96 [0.92-1.01]	0.83 [0.80-0.87]	<0.001
Rofecoxib	473	97.3	4.86	2.59 [2.35-2.87]	1.59 [1.43-1.75]	<0.001
Celecoxib	444	119	3.74	1.98 [1.79-2.20]	1.23 [1.11-1.36]	<0.001
Diclofenac	1008	439	2.3	1.22 [1.13-1.32]	1.20 [1.12-1.30]	<0.001
Naproxen	181	89.1	2.03	1.08 [0.93-1.26]	0.99 [0.86-1.16]	0.988
Other	1086	459.4	2.37	1.26 [1.17-1.36]	1.02 [0.95-1.10]	0.582
Fatal and non fatal stroke						
Ibuprofen	1139	1100	1.03	Ref.	Ref.	Ref.
No NSAID	18055	19000	0.97	0.95 [0.90-1.01]	0.83 [0.78-0.88]	<0.001
Rofecoxib	264	98.6	2.68	2.61 [2.29-2.99]	1.57 [1.37-1.80]	<0.001
Celecoxib	213	120.3	1.77	1.72 [1.49-1.99]	1.04 [0.90-1.21]	0.557
Diclofenac	528	441.9	1.19	1.16 [1.05-1.29]	1.14 [1.03-1.26]	0.012
Naproxen	98	89.6	1.09	1.06 [0.86-1.30]	0.98 [0.79-1.20]	0.814
Other	592	462.4	1.28	1.25 [1.13-1.39]	0.99 [0.90-1.10]	0.904
Fatal and non fatal myocardial infarction						
Ibuprofen	969	1100	0.87	Ref.	Ref.	Ref.
No NSAID	15504	19000	0.82	0.96 [0.90-1.03]	0.82 [0.77-0.88]	<0.001
Rofecoxib	205	99.8	2.05	2.37 [2.04-2.75]	1.48 [1.27-1.72]	<0.001
Celecoxib	211	121.5	1.74	2.00 [1.72-2.32]	1.25 [1.08-1.45]	0.003
Diclofenac	496	444.2	1.12	1.28 [1.15-1.43]	1.27 [1.14-1.41]	<0.001
Naproxen	82	90.2	0.91	1.05 [0.83-1.31]	0.96 [0.77-1.21]	0.753
Other	513	465.6	1.1	1.27 [1.14-1.41]	1.04 [0.93-1.16]	0.467
Cardiovascular death						
Ibuprofen	642	1100	0.58	Ref.	Ref.	Ref.
No NSAID	13317	19000	0.7	1.23 [1.14-1.33]	0.95 [0.87-1.03]	0.186
Rofecoxib	200	101.2	1.98	3.44 [2.93-4.03]	1.68 [1.43-1.97]	<0.001
Celecoxib	210	122.7	1.71	2.97 [2.54-3.47]	1.42 [1.22-1.66]	<0.001
Diclofenac	326	447	0.73	1.27 [1.11-1.45]	1.29 [1.13-1.47]	<0.001
Naproxen	66	90.7	0.73	1.27 [0.99-1.64]	1.16 [0.90-1.49]	0.239
Other	440	468.2	0.88	1.53 [1.35-1.73]	1.12 [0.99-1.27]	0.076

*** per 1000 person years**

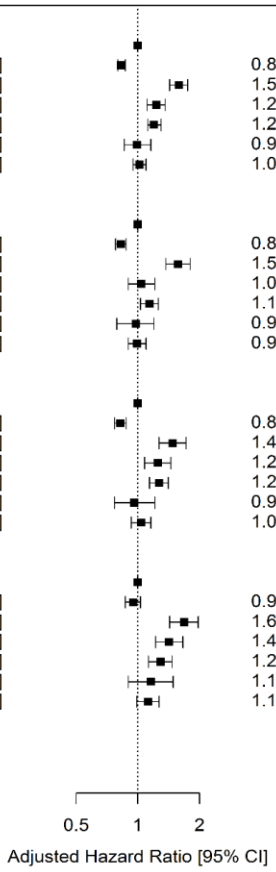

Figure 5

Groups	Events	Person Years	Incidence rate*	Unadjusted HR [95% CI]	Adjusted HR [95% CI]	p-value
Composite outcome						
Celecoxib	444	119	3.74	Ref.	Ref.	Ref.
No NSAID	32960	19000	1.78	0.96 [0.92-1.01]	0.68 [0.62-0.75]	<0.001
Rofecoxib	473	97.3	4.86	1.31 [1.15-1.49]	1.29 [1.14-1.47]	<0.001
Diclofenac	1008	439	2.3	0.62 [0.55-0.69]	0.98 [0.88-1.10]	<0.732
Ibuprofen	2071	1100	1.89	0.50 [0.46-0.56]	0.81 [0.74-0.90]	0.001
Naproxen	181	89.1	2.03	0.54 [0.46-0.65]	0.81 [0.68-0.97]	0.019
Other	1086	459.4	2.37	0.64 [0.57-0.71]	0.83 [0.74-0.93]	0.001
Fatal and non fatal stroke						
Celecoxib	213	120.3	1.77	Ref.	Ref.	Ref.
No NSAID	18055	19000	0.97	0.55 [0.48-0.63]	0.78 [0.69-0.91]	<0.001
Rofecoxib	264	98.6	2.68	1.52 [1.27-1.82]	1.50 [1.25-1.79]	<0.001
Diclofenac	528	441.9	1.19	0.67 [0.58-0.79]	1.09 [0.91-1.28]	0.281
Ibuprofen	1139	1100	1.03	0.58 [0.50-0.67]	0.96 [0.83-1.11]	0.557
Naproxen	98	89.6	1.09	0.62 [0.48-0.78]	0.93 [0.73-1.19]	0.573
Other	592	462.4	1.28	0.73 [0.62-0.85]	0.95 [0.81-1.11]	0.531
Fatal and non fatal myocardial infarction						
Celecoxib	212	121.3	1.75	Ref.	Ref.	Ref.
No NSAID	15504	19000	0.82	0.48 [0.42-0.55]	0.66 [0.57-0.75]	<0.001
Rofecoxib	205	99.8	2.05	1.19 [0.98-1.44]	1.19 [1.02-1.43]	0.025
Diclofenac	496	444.2	1.12	0.64 [0.55-0.76]	1.01 [0.86-1.19]	0.870
Ibuprofen	969	1100	0.87	0.50 [0.43-0.58]	0.80 [0.69-0.93]	0.003
Naproxen	82	90.2	0.91	0.52 [0.41-0.68]	0.77 [0.60-0.99]	0.045
Other	513	465.6	1.1	0.64 [0.54-0.75]	0.83 [0.71-0.98]	0.024
Cardiovascular death						
Celecoxib	210	122.7	1.71	Ref.	Ref.	Ref.
No NSAID	13317	19000	0.7	1.23 [1.14-1.33]	0.67 [0.58-0.76]	<0.001
Rofecoxib	200	101.2	1.98	1.16 [0.95-1.41]	1.18 [1.02-1.43]	0.042
Diclofenac	326	447	0.73	0.43 [0.36-0.51]	0.90 [0.76-1.08]	0.271
Ibuprofen	642	1100	0.58	0.34 [0.29-0.39]	0.70 [0.60-0.82]	<0.001
Naproxen	66	90.7	0.73	0.43 [0.32-0.56]	0.79 [0.67-0.93]	0.005
Other	440	468.2	0.88	0.52 [0.44-0.61]	0.82 [0.62-1.08]	0.156